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Palladium-Catalyzed Cyclobutanation of Aryl Sulfonates through both C−O and C−H Cleavage

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Cite This: https://dx.doi.org/10.1021/acs.organomet.0c00338 Read Online

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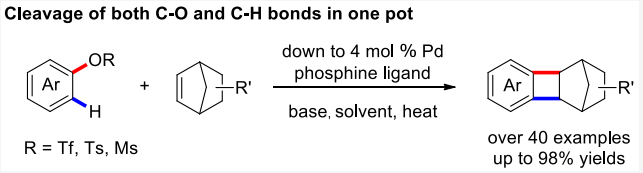
ABSTRACT: A palladium-catalyzed cyclobutanation of aryl sulfonates with strained alkenes has been developed. The methodology is featured to achieve the cleavage of both C−O and C−H bonds of phenol derivatives in one pot. Under the reaction conditions, in addition to reactive triflates, the relatively inactive tosylates and mesylates can also be transformed into the corresponding benzocyclobutanes in high yields. This reaction can be carried out in gram-scale experiments with a low loading of the palladium catalyst and is applicable to the cyclobutanative modification of bioactive molecules, highlighting its synthetic value in organic synthesis.

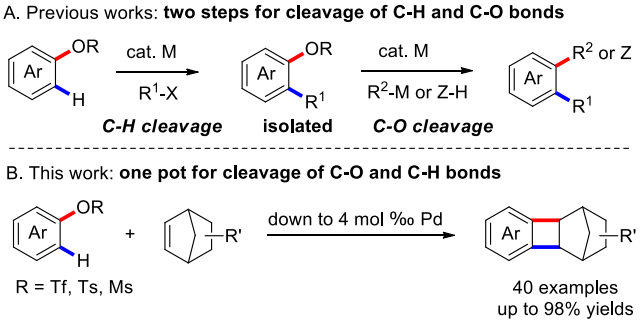


INTRODUCTION

Phenol derivatives are abundant in both nature and the synthetic world.[1] Owing to their easy availability and low toxicity, utilization of these compounds to produce value-added chemicals has drawn much attention in organic synthesis.[2] Recent advances have demonstrated that phenol derivatives could be used as efficient electrophiles instead of organohalides to couple with organometals (B, Mg, Zn, etc.) and Z−H (Z = C, N, P) compounds through transition-metal-catalyzed cleavage of C−O bonds, building the corresponding carbon−carbon and carbon−heteroatom bonds.[3,4] On the other hand, much effort has also been devoted to regioselective installation of a functional group at the benzene ring of phenol derivatives via C−H activation and ortho metalation.[5] The combination of the two strategies enables phenol derivatives to act as an excellent aryl source, and many polysubstituted aromatics have been produced by sequential cleavage of C−H and C−O bonds. However, to the best of our knowledge, all of the established reactions took place through two steps (Scheme 1A).

We envision that if the functionalization of C−H and C−O bonds could proceed in one pot, avoiding isolation and purification of the synthetic intermediates, the diversity of molecules would be greatly facilitated with higher synthetic efficiency. Herein, we report such a reaction to achieve the cyclobutanation of phenol derivatives (Scheme 1B). Our strategy toward the transformation is based on Heck-type reactions, which have been widely employed in transition-metal-catalyzed addition, reduction, and difunctionalization of alkenes.[6,7] During the reaction, the key point is to overcome the β-hydride elimination of Heck-type intermediate **C** generated in situ (Scheme 2). Thus, species **C** can further undergo intramolecular ligand exchange to generate **D**, followed by reductive elimination to produce the target product. Along this line, a variety of aryl sulfonates, including

Scheme 1. Transition-Metal-Catalyzed Functionalization of C−O and C−H Bonds of Phenol Derivatives



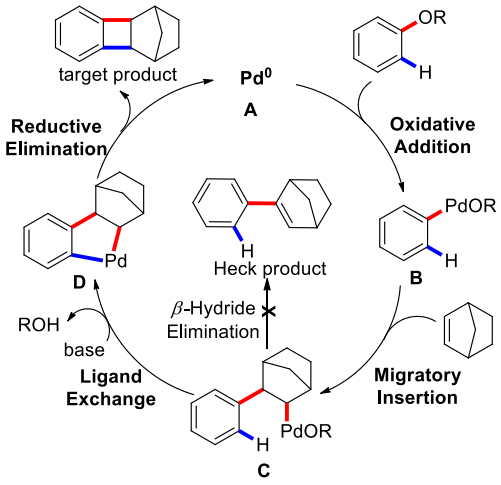
reactive triflates and relatively inactive tosylates and mesylates, were all readily cyclobutanated with strained alkenes by splitting both C−O and C−H bonds, providing an efficient method for preparing benzocyclobutananes. Benzocyclobutananes are building blocks of high value occurring in many functional molecules such as drugs and materials,[8] while their synthesis highly depended on the transformation of organohalides or special aromatics bearing a directing group.[8d,e,9−11]

RESULTS AND DISCUSSION

At 100 °C, a mixture of 1-naphthyl triflate (**1a**) and an alkene (**2a**, 1.5 equiv) was allowed to react in the presence of 0.5 mol % of $Pd_2(dba)_3$, 2 mol % of PPh_3, and 2 equiv of K_2CO_3 at 100

Received: May 14, 2020

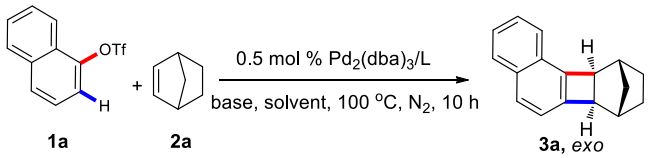
Scheme 2. Designed Reaction Path for Cleavage of C−O and C−H Bonds



°C in dioxane for 10 h; the corresponding product **3a** was produced in 98% yield (Table 1, entry 1). This reaction also took place readily with Pd(II) catalyst (Table 1, entry 2). However, in the absence of palladium catalyst, no reaction could be observed (Table 1, entry 3). The use of a phosphine ligand greatly influenced the transformation. The yields decreased with PCy_3, TFP, dpph, and XPhos (Table 1, entries 4, 5, 9, and 10), while almost no reaction occurred with dppm, dppp, and dppf (Table 1, entries 6−8). For the base, a suitable alkalinity was essential. K_3PO_4 showed an effect comparable to that of K_2CO_3 (Table 1, entry 13). The stronger base *t*-BuOK led to decomposition of the starting **1a** under the reaction conditions (Table 1, entry 11). Probably due to their low ability to assist in the activation of C−H bonds, weaker bases such as Na_2CO_3 and KOAc could not promote the reaction (Table 1, entries 14 and 15). With regard to solvent, the cyclobutanation reaction also proceeded efficiently in toluene, *p*-xylene, and cyclohexane but poorly in DCE (1,2-dichloroethane) and acetonitrile (Table 1, entries 16−20). Finally, lowering the reaction temperature to 90 °C led to a quick decrease in the yield (Table 1, entry 21).

This reaction is a general method for the synthesis of benzocyclobutananes. As shown in Table 2, a wide range of aryl triflates reacted with strained alkenes under mild reaction conditions to produce the cyclobutanated products in high yields through the cleavage of both C−O and C−H bonds in one pot. Thus, 1-naphthyl triflates including those bearing functional groups (**1a−c**) and 5-quinolinyl triflate (**1d**) all gave the expected products in excellent yields. High yield was also obtained from 2-naphthyl triflates (**1e**), but the reaction suffered from a regioselective issue due to the competitive activation between α-C−H and β-C−H bonds. To our delight, **3e** could be produced regioselectively with the use of CyJohnPhos ((2-biphenyl)dicyclohexylphosphine) as a ligand instead. The high selectivity might be attributed to the high steric hindrance of CyJohnPhos, making the intramolecular ligand exchange to occur preferentially at the less sterically hindered β-position. By slight tuning of the reaction conditions, both electron-rich and electron-deficient phenyl triflates served as the right substrates. Derivatives with 4-MeO, 4-*t*-Bu, and 4-Me (**1f−h**) were readily cyclobutanated. Substrates with high hindrance (**1i,j**) were also transformed into the corresponding benzocyclobutanes in high yields. As

Table 1. Palladium-Catalyzed Cyclobutanation Reaction of 1-Naphthyl Triflate with Norbornene[a]



entry	ligand	base	solvent	yield of **3a** (%)[b]	recovery of **1a** (%)[b]
1	PPh_3	K_2CO_3	dioxane	98	nd
2[c]		K_2CO_3	dioxane	94	nd
3[d]	PPh_3	K_2CO_3	dioxane	nd	81
4	PCy_3	K_2CO_3	dioxane	nd	80
5	TFP	K_2CO_3	dioxane	14	65
6	dppm	K_2CO_3	dioxane	trace	83
7	dppp	K_2CO_3	dioxane	nd	80
8	dppf	K_2CO_3	dioxane	trace	77
9	dpph	K_2CO_3	dioxane	55	30
10	Xphos	K_2CO_3	dioxane	92	nd
11	PPh_3	*t*-BuOK	dioxane	trace	trace
12	PPh_3	Cs_2CO_3	dioxane	50	trace
13	PPh_3	K_3PO_4	dioxane	90	trace
14	PPh_3	Na_2CO_3	dioxane	43	34
15	PPh_3	KOAc	dioxane	trace	73
16	PPh_3	K_2CO_3	toluene	95	nd
17	PPh_3	K_2CO_3	*p*-xylene	91	nd
18	PPh_3	K_2CO_3	DCE	57	30
19	PPh_3	K_2CO_3	cyclohexane	88	nd
20	PPh_3	K_2CO_3	MeCN	trace	89
21[e]	PPh_3	K_2CO_3	dioxane	93	11

[a]Reaction conditions unless specified otherwise: triflate **1a** (0.4 mmol), alkene **2a** (0.6 mmol), 0.5 mol % of $Pd_2(dba)_3$, phosphine ligand (Pd:P = 1:2), 2 equiv of base, solvent (1 mL), 100 °C, N_2 atmosphere, 10 h. Abbreviations: TFP, tris(2-furyl)phosphine; dppm, bis(diphenylphosphino)methane; dppp, 1,3-bis(diphenylphosphino)-propane; dppf, 1,1′-bis(diphenylphosphino)ferrocene; dpph, 1,6-bis(diphenylphosphino)hexane; XPhos, (2-(2,4,6-triisopropylphenethyl)phenyl)dicyclohexylphosphine. [b]GC yield using dodecane as an internal standard. [c]$Pd(PPh_3)_2Cl_2$ was used. [d]In the absence of Pd catalyst. [e]90 °C.

exemplified by **1l** as well as **1c**, the halo groups (F and Cl) survived well under the present conditions, facilitating further functionalization of the products via cross coupling. Phenyl triflates bearing electron-withdrawing CN and NO_2 groups (**1m,n**) have also proved to be good substrates.

Notably, this reaction was applicable to the cyclobutanative modification of bioactive phenol derivatives which are widely used in social production and life. For example, eugenol after sulfonylation was readily cyclobutanated chemoselectively to give **3o** in 91% yield with the valuable alkene unit being intact. A 95% yield of **3p** was also obtained from methyl vanillate under similar reaction conditions. Hordenine and raspberry ketone are also natural phenolic molecules, and their corresponding products (**3q,r**) were also produced in high yields in the current cyclobutanative system.

Importantly, other functionalized strained alkenes were applicable to this reaction. Thus, in addition to **2a**, strained alkenes bearing CN and even COOH groups also readily reacted with **1a** to produce the expected benzocyclobutananes **3s,t** in 75% and 65% yields, respectively. Similar cyclobutanation also took place with dicyclopentadiene and 2,5-

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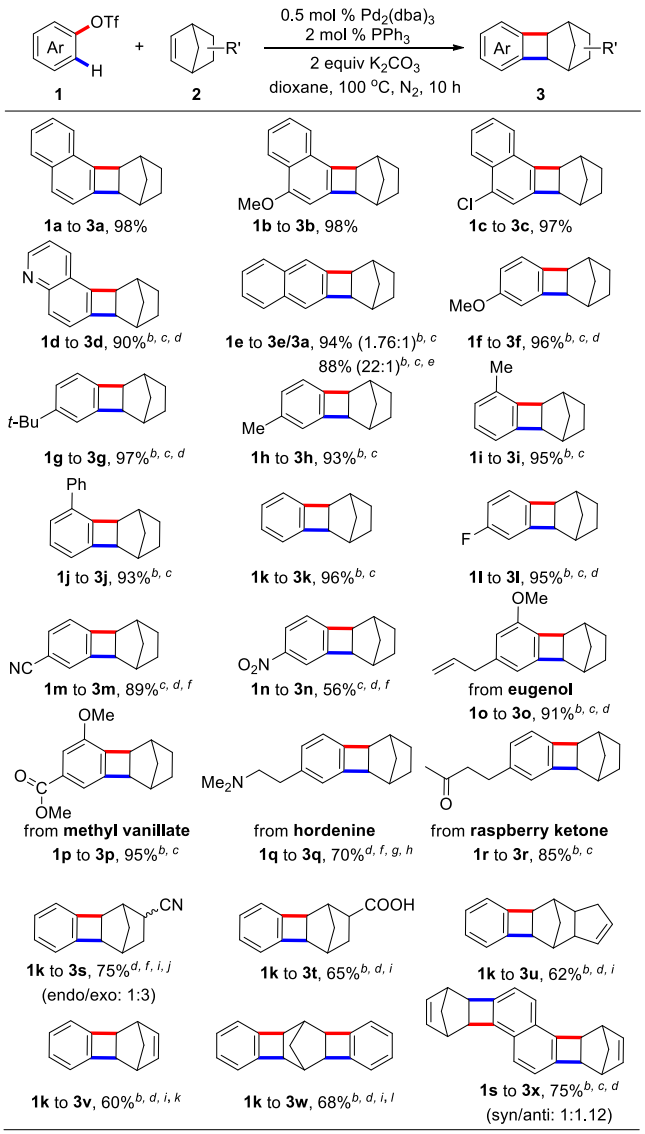
Table 2. Palladium-Catalyzed Cyclobutanation of Triflates with Strained Alkenes[a]

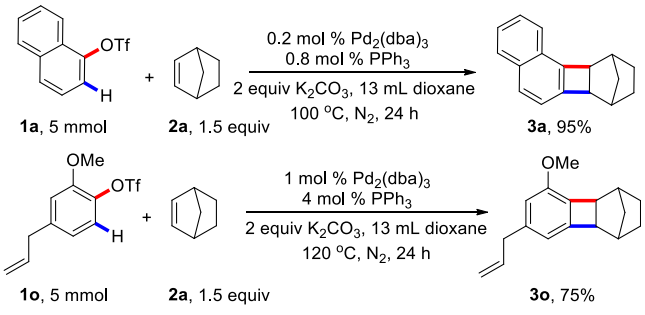


[a]Reaction conditions unless specified otherwise: aryl triflate (1, 0.4 mmol), alkene (2, 1.5 equiv), 0.5 mol % of $Pd_2(dba)_3$, PPh_3 (Pd:P = 1:2), 2 equiv of K_2CO_3, dioxane (1 mL), 100 °C, 10 h. Isolated yields. [b]20 °C. [c]15 h. [d]1 mol % of $Pd_2(dba)_3$. [e]CyJohnPhos as the ligand. [f]150 °C. [g]24 h. [h]Toluene as the solvent. [i]20 h. [j]The alkene substrate is a mixture (*endo*:*exo* = 1:2.8). [k]2.3 equiv of alkene. [l]0.5 equiv of alkene.

norbornadiene. Interestingly, by adjustment of the ratio of starting materials, both of the double bonds in 2,5-norbornadiene could participate in the reaction to give the dicyclobutanation product **3w** in good yield. As illustrated by **1s**, a bis-triflate could also be successfully dicyclobutanated with 2,5-norbornadiene in one pot, giving the expected product **3x** (a mixture of stereoisomers) in 75% yield. It would be imaginable that further cyclobutanation of **3x** with a bis-triflate under suitable reaction conditions would produce an interesting ladder-type polymer.

This reaction could also be conducted on a gram scale (Scheme 3). By heating of a mixture of 1-naphthyl triflate (**1a**; 5 mmol) and an alkene (**2a**; 1.5 equiv) in 13 mL of dioxane in the presence of 0.2 mol % of $Pd_2(dba)_3$, 0.8 mol % of PPh_3, and 2 equiv of K_2CO_3 at 100 °C for 24 h, **1a** was completely

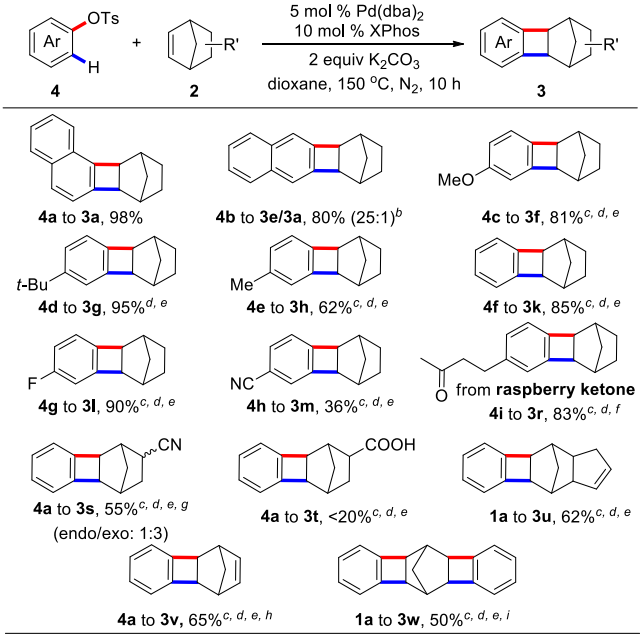
Scheme 3. Gram-Scale Experiments



converted into **3a**. After evaporation and passing of the residue of the reaction mixture through a SiO_2 column using hexane as an eluent, analytically pure **3a** was obtained in 95% isolated yield. The cyclobutanation of eugenol triflate could also be carried out on a 5 mmol scale, producing the expected **3o** in 75% isolated yield.

In comparison with those of triflates, C−O bonds of tosylates are less reactive. To our delight, by elevation of the reaction temperature to 150 °C, the cyclobutanation of tosylates was also achieved in a $Pd(dba)_2$/XPhos catalytic system. As shown in Table 3, 1-naphthyl tosylate gave **3a** in

Table 3. Palladium-Catalyzed Cyclobutanation of Tosylates with Strained Alkenes[a]



[a]Reaction conditions unless specified otherwise: aryl tosylate (**4**, 0.2 mmol), alkene (**2**, 1.5 equiv), 5 mol % of $Pd(dba)_2$, XPhos (Pd:P = 1:2), 2 equiv of K_2CO_3, dioxane (1 mL), 150 °C, 10 h. Isolated yields. [b]15 h. [c]10 mol % of $Pd(dba)_2$. [d]160 °C. [e]24 h. [f]48 h. [g]The alkene substrate is a mixture (*endo*:*exo* ratio = 1:2.8). [h]2.3 equiv of alkene. [i]0.5 equiv of alkene.

98% yield under the reaction conditions. 2-Naphthyl tosylate was also applicable, and the expected **3e** was produced regioselectively. Similarly, the results could be ascribed to the high steric hindrance of the ligand XPhos. With the present strategy, phenyl tosylates including those bearing functional groups (**4c**−**i**) were also cyclobutanated with **2a**. Moderate

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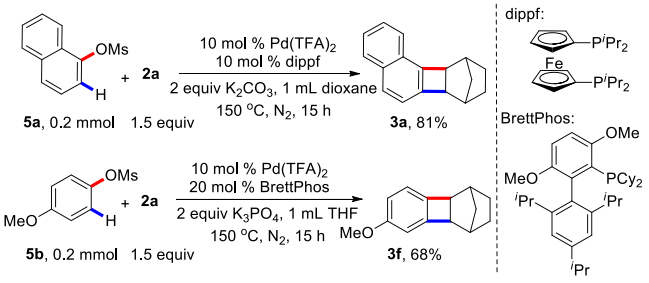
yields were also obtained with other selected strained alkenes except for those bearing a COOH group (**3s**−**v**). By similar adjustment of the loading of starting materials, phenyl tosylates could also react with 2,5-norbornadiene to give the dicyclobutanation product **3u**.

By using $Pd(TFA)_2$ and a suitable phosphine ligand as a catalyst (for details of the condition screening, see the Supporting Information), the more inactive mesylates were also transformed into the corresponding benzocyclobutanes via cleavage of both C−O and C−H bonds (Scheme 4). For

Scheme 4. Pd-Catalyzed Cyclobutanation of Mesylates with Strained Alkene 2a



example, with the use of $Pd(TFA)_2$/dippf as a catalyst, 1-naphthyl mesylate was readily cyclobutanated to produce **3a** in 81% yield. When the ligand was switched to BrettPhos and the base to K_3PO_4, 4-methoxyphenyl mesylate **5b** also served well, generating the corresponding benzocyclobutane **3f** in 68% yield.

CONCLUSIONS

In summary, we have disclosed a palladium-catalyzed cyclobutanation of sulfonates with strained alkenes through cleavage of both C−O and C−H bonds in one pot.[12] This reaction was rather general: in addition to reactive triflates, the relatively inactive tosylates and mesylates were also readily cyclobutanated. Many valuable functional groups such as Me, *t*-Bu, MeO, Ph, F, Cl, CN, NO_2, double bonds, esters, carbonyls, and even free COOH were all well tolerated under the reaction conditions. The application to the modification of bioactive molecules such as methyl vanillate, eugenol, raspberry ketone, and hordenine and the gram-scale experiments also well demonstrated the potential synthetic value of this new reaction.

EXPERIMENTAL SECTION

General Information. All experiments were carried out under a nitrogen atmosphere using standard Schlenk or dry glovebox techniques. Solvents were dried over Na metal or CaH_2 and were distilled under nitrogen prior to use. Reagents were of analytical grade and were obtained from commercial suppliers and used without further purification. Column chromatography was performed using silica gel 60 (300−400 mesh). The reactions were monitored by GC and GC-MS; GC-MS results were recorded on a GC-MS QP 2010 plus instrument, and GC analysis was performed on a GC 2014 instrument. The ^1H and ^{13}C NMR spectra were recorded on a Bruker ADVANCE III spectrometer at 400 and 100 MHz, respectively, and chemical shifts were reported in parts per million (ppm). High-resolution mass spectra (HRMS) were recorded on a LCMS-IT-TOF instrument by the ESI technique. All solvents and reagents were purchased from Energy Chemical, Alfa Aesar, and Aladdin.

General Procedure I for Synthesis of Aryl Triflates. To a solution of the phenol substrate (1.0 equiv, 0.5 M) in CH_2Cl_2 was added pyridine (2 equiv) at 0 °C. The mixture was allowed to stirred at 0 °C for 5 min followed by dropwise addition of Tf_2O (1.2 equiv). The reaction mixture was warmed to room temperature and stirred until full consumption of starting materials (monitored by TLC). The resulting mixture was concentrated under reduced pressure and purified by flash column chromatography.

General Procedure II for Synthesis of Aryl Tosylates. To a solution of the phenol substrate (20 mmol) in dichloromethane (80 mL) was added triethylamine (16 mL), the reaction mixture was cooled to 0 °C in an ice and water bath, and *p*-toluenesulfonyl chloride (24 mmol) was added portionwise. The reaction mixture was warmed to room temperature and stirred overnight. Water (25 mL) was then added and the resulting mixture was stirred for an additional 3 h. The mixture was then extracted with ethyl acetate (4 × 50 mL), and the organic layers were reunited, washed with water (3 × 50 mL), and dried over Na_2SO_4. The solvent was evaporated under vacuum. The resulting residue was purified by column chromatography or recrystallization.

General Procedure III for Synthesis of Aryl Mesylates. To a solution of the phenol substrate (1.0 equiv, 10.0 mmol) and Et_3N (1.5 equiv, 15.0 mmol) in CH_2Cl_2 (0.5 g/mL) was added dropwise a solution of MsCl (1.2 equiv, 12.0 mmol) at 0 °C. The mixture was warmed to room temperature and stirred for 4−12 h for the reaction completion. The reaction solution was added to H_2O (20 mL). The layers were separated, and the organic layer was extracted with water (10 mL × 2). The combined organic layers were dried over Na_2SO_4. After the solvent was evaporated, the product was purified by column chromatography over silica gel.

General Procedure IV for Synthesis of Arylcyclobutanes from Aryl Triflates. An oven-dried 10 mL Schlenk-type tube equipped with a magnetic stir bar was charged with aryl triflate (0.4 mmol), norbornene (56.5 mg, 1.5 equiv), $Pd_2(dba)_3$ (1.8 mg, 0.5 mol %), PPh_3 (2.1 mg, 2 mol %), and K_2CO_3 (110.6 mg, 2.0 equiv), followed by 1,4-dioxane (1.0 mL). The reaction tube was backfilled with nitrogen three times and well sealed. After the reaction mixture was stirred at 100 °C for 10 h, it was cooled to ambient temperature. The resulting mixture was diluted with CH_2Cl_2 (5 mL), dried over Na_2SO_4, and concentrated in vacuo. Products were obtained by preparative thin-layer chromatography (petroleum ether/ethyl acetate).

General Procedure V for Synthesis of Arylcyclobutanes from Aryl Tosylates. An oven-dried 10 mL Schlenk-type tube equipped with a magnetic stir bar was charged with aryl tosylate (0.2 mmol), norbornene (28.3 mg, 1.5 equiv), $Pd(dba)_2$ (5.8 mg, 5 mol %), XPhos (9.6 mg, 10 mol %), and K_2CO_3 (55.3 mg, 2.0 equiv), followed by 1,4-dioxane (1.0 mL). The reaction tube was backfilled with nitrogen three times and well sealed. After the reaction mixture was stirred at 150 °C for 10 h, it was cooled to ambient temperature. The resulting mixture was diluted with CH_2Cl_2 (5 mL), dried over Na_2SO_4, and concentrated in vacuo. The products were obtained by preparative thin-layer chromatography (petroleum ether/ethyl acetate).

General Procedure VI for Synthesis of Arylcyclobutanes from Aryl Mesylates. An oven-dried 10 mL Schlenk-type tube equipped with a magnetic stir bar was charged with 1-naphthyl mesylate (0.2 mmol), norbornene (28.3 mg, 1.5 equiv), $Pd(TFA)_2$ (6.6 mg, 10 mol %), dippf (8.4 mg, 10 mol %), and K_2CO_3 (55.3 mg, 2.0 equiv), followed by 1,4-dioxane (1.0 mL). The reaction tube was backfilled with nitrogen three times and well sealed. After the reaction mixture was stirred at 150 °C for 15 h, it was cooled to ambient temperature. The resulting mixture was diluted with CH_2Cl_2 (5 mL), dried over Na_2SO_4, and concentrated in vacuo. Products were obtained by preparative thin-layer chromatography (petroleum ether/ethyl acetate). When the ligand was switched to BrettPhos (21.5 mg, 20 mol %) and the base to K_3PO_4 (84.9 mg, 2.0 equiv), 4-methoxyphenyl mesylate (0.2 mmol) also served well.

*exo-6b,7,8,9,10,10a-Hexahydro-7,10-methanobenzo[a]biphenylene (**3a**).*[9i] The title compound was prepared according to the general procedure IV and purified by flash chromatography (hexanes) as a colorless oil (86 mg, 98%). ^1H NMR (400 MHz,

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$CDCl_3$): δ 7.97 (d, J = 8.0 Hz, 1H), 7.87−7.84 (m, 2H), 7.60−7.50 (m, 2H), 7.31 (d, J = 8.0 Hz, 1H), 3.56 (db, 1H), 3.41 (db, 1H), 2.55 (b, 1H), 2.43 (b, 1H), 1.81−1.76 (m, 2H), 1.43−1.35 (m, 2H), 1.07 (db, 1H), 0.89 (db, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.3, 142.0, 133.2, 129.5, 129.0, 128.0, 126.0, 124.7, 122.4, 121.0, 50.1, 49.3, 35.91, 35.87, 31.9, 28.1, 28.0.

*exo-5-Methoxy-6b,7,8,9,10,10a-hexahydro-7,10-methanobenzo-[a]biphenylene (**3b**).* The title compound was prepared according to the general procedure IV and purified by flash chromatography (hexanes) as a colorless oil (98 mg, 98%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56 (d, J = 8.0 Hz, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.69−7.59 (m, 2H), 6.77 (s, 1H), 4.11 (s, 3H), 3.57 (db, 1H), 3.44 (db, 1H), 2.60 (b, 1H), 2.48 (b, 1H), 1.87−1.84 (m, 2H), 1.47−1.44 (m, 2H), 1.15 (db, 1H), 1.01 (db, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.4, 143.0, 133.5, 130.1, 126.7, 125.9, 124.2, 123.7, 122.3, 99.7, 55.8, 50.3, 49.1, 36.2, 35.9, 32.0, 28.4, 28.1. HRMS (ESI, m/z): $[M + H]^+$ calcdfor $C_{18}H_{19}O$ 251.1436, found 251.1430.

*exo-5-Chloro-6b,7,8,9,10,10a-hexahydro-7,10-methanobenzo-[a]biphenylene (**3c**).* The title compound was prepared according to the general procedure IV and purified by flash chromatography (hexanes) as a colorless oil (99 mg, 97%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30−8.28 (m, 1H), 7.68−7.65 (m, 1H), 7.47−7.44 (m, 2H), 7.26 (s, 1H), 3.34 (db, 1H), 3.21 (db, 1H), 2.35 (b, 1H), 2.23 (b, 1H), 1.62−1.58 (m, 2H), 1.24−1.15 (m, 2H), 0.90 (db, 1H), 0.71 (db, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.9, 141.3, 131.5, 130.6, 130.2, 126.8, 126.02, 125.95, 122.9, 121.8, 50.4, 49.4, 35.94, 35.86, 31.9, 28.1, 28.0. HRMS (ESI, m/z): $[M + H]^+$ calcd for $C_{17}H_{16}Cl$: 255.0941, found 255.0937.

*exo-6b,7,8,9,10,10a-Hexahydro-7,10-methanobenzo[3,4]-cyclobuta[1,2-f]quinoline (**3d**).* The title compound was prepared according to the general procedure IV and purified by flash chromatography (hexanes) as a colorless oil (80 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.85 (dd, J_1 = 2.0 Hz, J_2 = 4.4 Hz, 1H), 8.04 (db, 1H), 7.99 (d, J = 8.4 Hz, 1H), 7.41 (d, J = 8.4 Hz, 1H), 7.35 (dd, J_1 = 4.4 Hz, J_2 = 8.4 Hz, 1H), 3.41 (db, 1H), 3.30 (db, 1H), 2.39 (b, 1H), 2.32 (b, 1H), 1.68−1.65 (m, 2H), 1.28−1.25 (m, 2H), 0.96 (db, 1H), 0.70 (db, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.2, 148.3, 144.0, 141.8, 130.7, 129.7, 124.6, 124.1, 121.0, 50.1, 49.0, 36.0, 35.8, 31.8, 28.0, 27.9. HRMS (ESI, m/z): $[M + H]^+$ calcd for $C_{16}H_{16}N$ 222.1283, found 222.1275.

*exo-1,2,3,4,4a,10b-Hexahydro-1,4-methanobenzo[b]-biphenylene (**3e**).*[9i] The title compound was prepared according to the general procedure IV and purified by flash chromatography (hexanes) as a white solid (83 mg, 94%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81−7.79 (m, 2H), 7.42 (s, 2H), 7.41−7.38 (m, 2H), 3.37 (b, 2H), 2.41 (b, 2H), 1.64 (db, 2H), 1.28−1.26 (m, 2H), 1.04−0.96 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.8, 134.2, 128.1, 124.5, 119.7, 50.4, 37.7, 32.4, 27.9.

*exo-6-Methoxy-1,2,3,4,4a,8b-hexahydro-1,4-methanobiphenylene (**3f**).*[9i] The title compound was prepared according to the general procedure IV and purified by flash chromatography (hexanes) as a colorless oil (77 mg, 96%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.91 (d, J = 8.0 Hz, 1H), 6.75 (dd, J_1 = 2.0 Hz, J_2 = 8.0 Hz, 1H), 6.61 (d, J = 2.0 Hz, 1H), 3.78 (s, 3H), 3.11 (b, 2H), 2.24 (b, 2H), 1.60−1.58 (m, 2H), 1.18−1.16 (m, 2H), 0.96 (db, 1H), 0.87 (db, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.7, 147.3, 138.3, 122.9, 113.7, 107.7, 55.4, 49.7, 49.6, 36.9, 36.6, 32.0, 27.9, 27.8.

*exo-6-(tert-Butyl)-1,2,3,4,4a,8b-hexahydro-1,4-methanobiphenylene (**3g**).*[9i] The title compound was prepared according to the general procedure IV and purified by flash chromatography (hexanes) as a colorless oil (88 mg, 97%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (d, J = 6.8 Hz, 1H), 7.11 (s, 1H), 7.00 (d, J = 8.0 Hz, 1H), 3.21 (db, 2H), 2.33 (b, 2H), 1.66 (db, 2H), 1.37 (s, 9H), 1.25−1.23 (m, 2H), 1.02 (db, 1H), 0.94 (db, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.5, 146.3, 143.6, 124.4, 121.6, 118.9, 50.5, 50.2, 36.9, 36.8, 35.2, 32.3, 32.0, 28.1 (two overlapping signals).

*exo-5-Phenyl-1,2,3,4,4a,8b-hexahydro-1,4-methanobiphenylene (**3h**).*[9g] The title compound was prepared according to the general procedure IV and purified by flash chromatography (hexanes) as a colorless oil (66 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (d, J = 7.2 Hz, 1H), 7.18 (d, J = 7.6 Hz, 1H), 7.12 (s, 1H), 3.44 (b, 2H), 2.63 (s, 3H), 2.55 (b, 2H), 1.90−1.88 (m, 2H), 1.49−1.46 (m, 2H), 1.27−1.20 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.7, 143.6, 136.9, 128.2, 122.8, 121.9, 50.4, 50.2, 37.01, 36.95, 32.3, 28.23, 28.17, 22.4.

*exo-5-Methyl-1,2,3,4,4a,8b-hexahydro-1,4-methanobiphenylene (**3i**).*[9i] The title compound was prepared according to the general procedure IV and purified by flash chromatography (hexanes) as a colorless oil (70 mg, 95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18 (dd, J_1 = 7.6 Hz, J_2 = 7.2 Hz, 1H), 7.05 (d, J = 7.6 Hz, 1H), 6.89 (d, J = 7.2 Hz, 1H), 3.22 (dd, J_1 = 3.6 Hz, J_2 = 7.6 Hz, 2H), 2.37 (b, 1H), 2.33 (b, 1H), 2.26 (s, 3H), 1.70−1.65 (m, 2H), 1.29−1.23 (m, 2H), 1.04 (db, 1H), 0.93 (db, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.1, 145.0, 132.0, 127.9, 127.6, 119.1, 49.8, 49.6, 36.5, 35.8, 32.1, 27.91, 27.85, 16.6.

*exo-5-Phenyl-1,2,3,4,4a,8b-hexahydro-1,4-methanobiphenylene (**3j**).*[9g] The title compound was prepared according to the general procedure IV and purified by flash chromatography (hexanes) as a white solid (92 mg, 93%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, J = 7.2 Hz, 2H), 7.49−7.41 (m, 3H), 7.33−7.27 (m, 2H), 6.96 (d, J = 7.2 Hz, 1H), 3.45 (db, 1H), 3.23 (db, 1H), 2.36 (b, 1H), 2.32 (b, 1H), 1.62 (db, 2H), 1.26−1.22 (m, 2H), 1.00−0.94 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.2, 143.4, 138.3, 134.6, 128.7 (two overlapping signals), 128.2, 127.2, 126.9 (two overlapping signals), 124.8, 120.8, 51.5, 50.1, 36.7, 36.2, 32.1, 27.89, 27.85.

*exo-1,2,3,4,4a,8b-Hexahydro-1,4-methanobiphenylene (**3k**).*[9i] The title compound was prepared according to the general procedure IV and purified by flash chromatography (hexanes) as a colorless oil (65 mg, 96%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33−7.31 (m, 2H), 7.14−7.12 (m, 2H), 3.31 (b, 2H), 2.40 (b, 2H), 1.73 (db, 2H), 1.33−1.30 (m, 2H), 1.10 (db, 1H), 1.00 (db, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.6, 127.2, 121.9, 50.5, 36.7, 32.0, 27.9.

*exo-6-Fluoro-1,2,3,4,4a,8b-hexahydro-1,4-methanobiphenylene (**3l**).*[9f] The title compound was prepared according to the general procedure IV and purified by flash chromatography (hexanes) as a colorless oil (71 mg, 95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.97−6.87 (m, 2H), 6.75 (dd, J_1 = 2.0 Hz, J_1 = 8.0 Hz, 1H), 3.15 (b, 2H), 2.28 (db, 2H), 1.65−1.59 (m, 2H), 1.23−1.17 (m, 2H), 1.00 (db, 1H), 0.87 (db, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.1, 161.7, 147.61, 147.55, 141.55, 141.52, 123.4, 123.3, 114.5, 114.3, 109.8, 109.6, 49.55, 49.51, 36.7, 36.4, 31.8, 27.74, 27.65.

*exo-1,2,3,4,4a,8b-Hexahydro-1,4-methanobiphenylene-6-carbonitrile (**3m**).*[9f] The title compound was prepared according to the general procedure IV and purified by flash chromatography (hexanes) as a colorless oil (69 mg, 89%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (dd, J_1 = 1.2 Hz, J_1 = 7.6 Hz, 1H), 7.28 (s, 1H), 7.11 (d, J = 7.6 Hz, 1H), 3.27−3.24 (m, 2H), 2.33 (db, 2H), 1.65−1.63 (m, 2H), 1.23−1.21 (m, 2H), 1.03 (db, 1H), 0.81 (db, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.1, 147.3, 131.9, 125.3, 122.8, 119.8, 110.8, 51.0, 50.4, 36.5 (2 overlapping signals), 31.9, 27.6, 27.5.

*exo-6-Nitro-1,2,3,4,4a,8b-hexahydro-1,4-methanobiphenylene (**3n**).*[9f] The title compound was prepared according to the general procedure IV and purified by flash chromatography (hexanes) as yellow oil (48 mg, 56%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (dd, J_1 = 2.0 Hz, J_1 = 8.0 Hz, 1H), 7.84 (d, J = 1.6 Hz, 1H), 7.12 (d, J = 8.0 Hz, 1H), 3.25 (b, 2H), 2.34 (b, 2H), 1.66−1.60 (m, 2H), 1.24−1.19 (m, 2H), 1.02 (db, 1H), 0.79 (db, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.4, 148.1, 147.3, 123.6, 122.7, 117.5, 50.5, 49.9, 36.6, 36.5, 31.9, 27.6, 27.5.

*exo-7-Allyl-5-methoxy-1,2,3,4,4a,8b-hexahydro-1,4-methanobiphenylene (**3o**).* The title compound was prepared according to the general procedure IV and purified by flash chromatography (hexanes) as a colorless oil (87 mg, 91%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.52 (s, 1H), 6.47 (s, 1H), 5.99−5.89 (m, 1H), 5.09−5.02 (m, 2H), 3.88 (s, 3H), 3.31 (d, J = 6.8 Hz, 2H), 3.26 (db, 1H), 3.12 (db, 1H), 2.30 (db, 1H), 2.25 (db, 1H), 1.62−1.59 (m, 2H), 1.21−1.16 (m, 2H), 1.04−0.99 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.4, 148.6, 141.5, 137.8, 126.5, 119.8, 115.5, 114.8, 114.1, 56.4, 50.2, 49.8, 40.7, 38.0, 36.6, 31.8, 27.8. HRMS (ESI, m/z): $[M + H]^+$ calcd for $C_{17}H_{21}O$ 241.1592, found 241.1582.

https://dx.doi.org/10.1021/acs.organomet.0c00338
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*exo-8-Methoxy-1,2,3,4,4a,8b-hexahydro-1,4-methanobiphenylene-6-carboxylate (**3p**).* The title compound was prepared according to the general procedure IV and purified by flash chromatography (hexanes) as a colorless oil (98 mg, 95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (s, 1H), 7.28 (s, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.28 (db, 1H), 3.15 (db, 1H), 2.33 (b, 1H), 2.27 (b, 1H), 1.65−1.56 (m, 2H), 1.22−1.16 (m, 2H), 1.00 (db, 1H), 0.93 (db, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.5, 153.4, 148.4, 134.9, 131.2, 115.9, 114.8, 56.3, 52.0, 50.0, 49.9, 37.5, 36.5, 31.8, 27.7, 27.6. HRMS (ESI, m/z): $[M + H]^+$ calcd for $C_{16}H_{19}O_3$ 259.1334, found 259.1334.

*exo-2-(1,2,3,4,4a,8b-Hexahydro-1,4-methanobiphenylen-6-yl)-N,N-dimethylethanamine (**3q**).* The title compound was prepared according to the general procedure IV and purified by flash chromatography (hexanes) as a colorless oil (68 mg, 70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.04−7.02 (m, 1H), 6.93 (db, 1H), 6.86 (s, 1H), 3.13−3.07 (m, 4H), 2.99−2.95 (m, 2H), 2.79 (s, 6H), 2.24 (b, 2H), 1.60−1.57 (m, 2H), 1.19−1.13 (m, 2H), 0.94 (db, 1H), 0.79 (db, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.6, 144.1, 139.4, 127.6, 122.2, 121.8, 62.2, 50.2, 50.0, 45.5 (2 overlapping signals), 36.7, 36.6, 35.1, 32.0, 27.84, 27.81. HRMS (ESI, m/z): $[M + H]^+$ calcd for $C_{17}H_{24}N$ 242.1909, found 242.1911.

*exo-4-(1,2,3,4,4a,8b-Hexahydro-1,4-methanobiphenylen-6-yl)-but-an-2-one (**3r**).* The title compound was prepared according to the general procedure IV and purified by flash chromatography (hexanes) as a colorless oil (82 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.01 (d, J = 7.6 Hz, 1H), 6.90 (d, J = 7.6 Hz, 1H), 6.82 (s, 1H), 3.13 (b, 2H), 2.88−2.84 (m, 2H), 2.74−2.71 (m, 2H), 2.24 (b, 2H), 2.13 (s, 3H), 1.60−1.55 (m, 2H), 1.19−1.14 (m, 2H), 0.95 (db, 1H), 0.83 (db, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.2, 146.8, 144.2, 140.0, 127.2, 121.9, 121.8, 50.1, 50.0, 45.8, 36.65, 36.58, 31.9, 30.5, 30.1, 27.81, 27.79. HRMS (ESI, m/z): $[M + H]^+$ calcd for $C_{17}H_{21}O$ 241.1592, found 241.1590.

*exo-1,2,3,4,4a,8b-Hexahydro-1,4-methanobiphenylene-2-carbonitrile (**3s**).* The title compound was prepared according to the general procedure IV and purified by flash chromatography (hexanes) as a yellow oil (59 mg, 75%). **3s** is an *endo*/*exo* mixture; the ratio is ca. 1:3 on the basis of ^{13}C NMR. ^{1}H NMR (400 MHz, $CDCl_3$; for clarity, the integration of H atoms is expanded by 4 times): δ 7.25−7.23 (m, 8H), 7.05−7.01 (m, 8H), 3.81 (db, 3H), 3.36 (db, 3H), 3.23 (b, 2H), 2.86−2.80 (m, 3H), 2.68 (b, 1H), 2.62−2.60 (m, 3H), 2.47−2.42 (m, 4H), 2.16−2.09 (m, 3H), 1.97−1.92 (m, 1H), 1.74−1.68 (m, 1H), 1.51−1.46 (m, 3H), 1.41−1.38 (m, 1H), 1.10−1.03 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.5 (144.8), 144.5 (145.3), 128.1 (127.92), 123.3 (127.92), 122.29 (127.89), 122.2 (122.26), 122.0 (122.1), 49.3 (49.6), 48.8 (45.8), 42.0 (39.8), 36.4 (36.7), 34.5 (33.6), 31.0 (32.5), 29.5 (29.0). HRMS (ESI, m/z): $[M + H]^+$ calcd for $C_{14}H_{14}N$ 196.1126, found 196.1121..

*exo-1,2,3,4,4a,8b-Hexahydro-1,4-methanobiphenylene-2-carboxylic acid (**3t**).* The title compound was prepared according to the general procedure IV and purified by flash chromatography (hexanes) as a yellow oil (56 mg, 65%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36−7.32 (m, 2H), 7.25−7.19 (m, 2H), 4.98 (db, 1H), 3.28−3.25 (m, 1H), 2.97 (b, 1H), 2.70 (db, 1H), 2.66−2.62 (m, 1H), 2.18−2.11 (m, 1H), 1.98−1.89 (m, 2H), 1.62−1.59 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 181.0, 141.2, 128.7, 127.1, 126.6, 86.7 (2 overlapping signals), 54.0 (2 overlapping signals), 46.6, 41.9, 39.1, 35.4, 35.2. HRMS (ESI, m/z): $[M + H]^+$ calcd for $C_{14}H_{15}O_2$ 215.1072, found 215.1062.

*exo-3a,4,4a,8b,9,9a-Hexahydro-1H-4,9-methanocyclopenta[b]-biphenylene (**3u**).*[9i] The title compound was prepared according to the general procedure IV and purified by flash chromatography (hexanes) as a white solid (52 mg, 62%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23−7.20 (m, 2H), 7.00−6.98 (m, 2H), 5.73−5.72 (m, 1H), 5.68−5.66 (m, 1H), 3.37 (db, 1H), 3.27 (db, 1H), 3.23−3.18 (m, 1H), 2.75−2.68 (m, 1H), 2.44−2.28 (m, 4H), 1.26−1.23 (m, 1H), 1.05 (db, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.0, 146.3, 131.4, 131.2, 127.1, 127.1, 121.9, 121.6, 52.3, 46.9, 44.1, 41.3, 40.8, 39.0, 35.5, 31.5.

*exo-1,4,4a,8b-Tetrahydro-1,4-methanobiphenylene (**3v**).*[11a] The title compound was prepared according to the general procedure IV and purified by flash chromatography (hexanes) as a colorless oil (40 mg, 60%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23−7.20 (m, 2H), 7.10−7.08 (m, 2H), 6.25−6.24 (m, 2H), 3.17 (b, 2H), 2.81 (b, 2H), 1.31 (db, 1H), 0.90 (db, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.2, 136.7, 127.0, 121.8, 47.6, 41.6, 41.4.

*exo,exo-4b,5,5a,9b,10,10a-hexahydro-5,10-methanobenzo[3,4]-cyclobuta[1,2-b]biphenylene (**3w**).*[11a] The title compound was prepared according to the general procedure IV and purified by flash chromatography (hexanes) as a white solid (66 mg, 68%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21−7.19 (m, 4H), 7.03−7.01 (m, 4H), 3.30 (b, 4H), 2.39 (b, 2H), 0.77 (b, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.4, 127.4, 122.0, 49.4, 37.3, 26.1.

*exo,exo-1,4,4a,6b,7,10,10a,12b-Octahydro-1,4:7,10-dimethanobiphenyleno[2,1-a]biphenylene (**3x**).* The title compound was prepared according to the general procedure IV and purified by flash chromatography (hexanes) as a white solid (92 mg, 75%). **3x** is a *syn*/*anti* mixture; the ratio is ca. 1:12 on the basis of GC analysis. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68−7.64 (m, 2H), 7.28−7.24 (m, 2H), 6.30−6.26 (m, 4H), 3.39−3.36 (m, 2H), 3.24−3.22 (m, 2H), 2.90 (db, 2H), 2.78 (b, 2H), 1.32−1.25 (m, 2H), 0.83−0.75 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.9 (142.8), 143.9 (142.7), 136.7 (136.5), 136.7 (128.5), 136.5 (128.4), 122.1 (120.9), 122.0 (120.8), 47.1 (41.5), 47.1 (41.4), 46.4 (40.79), 46.4 (40.76), 40.7 (40.7). HRMS (ESI, m/z): $[M + H]^+$ calcd for $C_{24}H_{21}$ 309.1643, found 309.1641.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information including . . The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.organomet.0c00338.

Optimization of the reactions and ^{1}H and ^{13}C NMR spectra (PDF)

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Complete contact information is available at: https://pubs.acs.org/10.1021/acs.organomet.0c00338

https://dx.doi.org/10.1021/acs.organomet.0c00338
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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Partial financial support from the NSFC (Grant Nos. 21871070 and 21403062) and the Fundamental Research Funds for the Central Universities (Hunan University) is gratefully acknowledged.

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